Complete Summary

GUIDELINE TITLE

The role of amifostine as a radioprotectant in the management of patients with squamous cell head and neck cancer.

BIBLIOGRAPHIC SOURCE(S)

Head and Neck Cancer Disease Site Group. Hodson DI, Browman GP, Thephamongkhol K, Oliver T, Zuraw L. The role of amifostine as a radioprotectant in the management of patients with squamous cell head and neck cancer [full report]. Toronto (ON): Cancer Care Ontario (CCO); 2004 Mar [online update]. 22 p. (Practice guideline report; no. 5-8). [26 references]

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

- Squamous cell head and neck cancer
- Conditions associated with side effects of radiotherapy in the head and neck region, including acute and chronic xerostomia and mucositis

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Management

CLINICAL SPECIALTY

Oncology
Radiation Oncology

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

To evaluate the role of amifostine to safely and effectively ameliorate important side effects of radiotherapy with acceptable toxicity and no tumour protection

TARGET POPULATION

Adult patients with any stage of squamous cell head and neck cancer who are receiving radical radiotherapy, encompassing at least 75% of the parotid glands, with or without concurrent chemotherapy

INTERVENTIONS AND PRACTICES CONSIDERED

Amifostine

MAJOR OUTCOMES CONSIDERED

Outcomes related to radiation-induced side effects, quality of life, or survival differences were reported. Xerostomia, mucositis, and the anti-tumour effects of amifostine were the main outcomes of interest. Tumour protection was inferred from differences in rates of response, local recurrence, and/or survival between the intervention group (with amifostine) and the control group (without amifostine).

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases
Searches of Unpublished Data

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Original Guideline: May 2003

The literature was searched using the MEDLINE (1966 through January 2003), CANCERLIT (1983 through October 2002), and Cochrane Library (Issue 4, 2002) databases. In addition, the Physician Data Query clinical trials database, and abstracts published in the conference proceedings from the meetings of the American Society of Clinical Oncology (1998-2002), the American Society for Therapeutic Radiology and Oncology (1999-2002), and the European Society for Medical Oncology (1998, 2000) were searched for reports of new or ongoing trials. The Canadian Medical Association Infobase and the National Guideline Clearinghouse databases were searched for clinical practice guidelines. Reference lists from relevant articles and reviews were searched for additional trials. In the

event of incomplete or missing data, authors were contacted for further information.

The literature search combined disease-specific terms (head and neck neoplasms/ or carcinoma, squamous cell/ or head and neck cancer.tw.) with treatment-specific terms (amifostine/ or amifostine.tw. or ethyol.tw. or wr-2721.tw.) and (radiotherapy/ or combined modality therapy/) with search-specific terms for the following study designs: practice guidelines, systematic reviews or meta-analyses, reviews, randomized controlled trials, and clinical trials.

Update

The original literature search has been updated using MEDLINE (January 2003 through March 2004), EMBASE (1980 through March 2004), the Cochrane Library (Issue 1, 2004), the Physician Data Query database, the Canadian Medical Association Infobase, and the National Guideline Clearinghouse, as well as abstracts published in the proceedings of the meetings of the American Society of Clinical Oncology (2003), the American Society for Therapeutic Radiology and Oncology (2003), and the European Society for Medical Oncology (2002). Article bibliographies and personal files were also searched to March 2004 for evidence relevant to this practice guideline report. Please note that CANCERLIT is no longer included in update searches: results from an internal PGI project indicated that the overlap with MEDLINE is 100%, making CANCERLIT database searches redundant.

Original Guideline: May 2003

Inclusion Criteria

Articles were selected for inclusion in this systematic review of the evidence if they were fully published reports or published abstracts that met the following criteria:

1. Randomized trials comparing conventionally fractionated radical radiotherapy or concurrent radiochemotherapy, encompassing at least 75% of the parotid glands, with or without amifostine in adult patients with any stage squamous cell head and neck cancer. Conventionally fractionated radiotherapy was defined as single daily fractions ranging from 1.8 to 2.5 Gy to a total of 5,000 to 7,400 cGy.
2. Practice guidelines, meta-analyses, or systematic reviews related to the guideline question
3. Outcomes related to radiation-induced side effects, quality of life, or survival differences were reported. Xerostomia, mucositis, and the anti-tumour effects of amifostine were the main outcomes of interest. Tumour protection was inferred from differences in rates of response, local recurrence, and/or survival between the intervention group (with amifostine) and the control group (without amifostine).

Update

Through the editorial process the second bullet was revised as a separate paragraph to read:

Practice guidelines, meta-analyses, or systematic reviews explicitly based on randomized trials to the guideline question were also eligible for inclusion.

Original Guideline: May 2003

Exclusion Criteria

1. Phase I and II studies were not considered.
2. Letters and editorials were not considered.
3. Papers published in a language other than English were not considered.

Update

Through the editorial process the document was modified to reflect the removal of the following two exclusion criteria:

- Phase I and II studies were not considered.
- Letters and editorials were not considered.

NUMBER OF SOURCE DOCUMENTS

Original Guideline: May 2003

Five randomized trials, one randomized trial presented as an abstract, one quality of life paper, and one practice guideline were reviewed.

Update

Two randomized trials were identified and included in the systematic review.

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus (Committee)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Meta-Analysis of Randomized Controlled Trials
Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Original Guideline: May 2003

To estimate the overall radioprotective effect of amifostine on mucositis and xerostomia, the results of the randomized trials were pooled using the meta-analytic software program RevMan 4.1 (Metaview © Update Software). For the event of interest, results are expressed as the odds ratio (OR) with 95% confidence intervals (CI) such that estimates <1.0 favour amifostine and estimates >1.0 favour control. Data were to be analyzed using both fixed-effect (Mantel-Haenszel) and random effect models. If statistical heterogeneity was identified ($p<0.1$), the more conservative estimate of effect, the random effects model, would be chosen. Heterogeneity was anticipated given the following trial differences:

- One large randomized trial and several small randomized trials
- Amifostine ranging from flat doses of 500 mg or 200mg/m^2 up to 300 mg/m^2
- Amifostine administered intravenously or subcutaneously
- Amifostine added to radiotherapy or radiochemotherapy
- Amifostine administered daily with radiotherapy or only on days of radiochemotherapy

Despite the anticipated heterogeneity with respect to trial quality, variation in amifostine administration, and use of chemotherapy, the hypothesis upon which amifostine use is based is the same. Therefore, it was considered appropriate by the Head and Neck Cancer Disease Site Group to examine the effects of amifostine across these trials.

In testing for publication bias, the funnel plots of the pooled data seemed to be asymmetric; however, two tests for publication bias, Begg´s test and Egger´s test, were negative (data not shown).

Update

The first and second bullets were revised through the editorial process to provide greater clarity and should now read:

- Trial size variations: one large randomized trial and several small randomized trials
- Amifostine ranging from flat doses of 500 mg or doses of 200mg/m^2 up to 300 mg/m^2

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Disease Site Group Consensus Process

The Head and Neck Cancer Disease Site Group (DSG) convened to discuss the evidence surrounding amifostine as a radioprotectant in the treatment of head and neck cancer. The best evidence comes from the large trial reported by Brizel et al investigating radiotherapy alone with or without amifostine. It was agreed

that the presentation of results from the small trials should be framed in this context. The DSG felt that the smaller studies were largely consistent with the trial reported by Brizel, which detected a significant reduction in acute and chronic xerostomia with amifostine. In terms of mucositis, the evidence was less conclusive. The large trial did not detect any significant difference in mucositis, while three of the small trials demonstrated a significant difference in mucositis favouring amifostine. Pooled results from the four trials detected a non-significant difference in mucositis favouring amifostine.

Given the evidence presented, the DSG felt that amifostine may be considered to reduce acute and chronic xerostomia associated with radical conventionally fractionated radiotherapy, with or without standard dose carboplatin, given to patients in the head and neck region. The data on mucositis are inconclusive.

The DSG identified several concerns with the use of amifostine in the context of clinical practice in Ontario. First, a common practice for suitable patients with stage III/IV squamous cell carcinoma in Ontario is a conventionally fractionated course of radiotherapy delivered concurrently with low-dose cisplatin or carboplatin. No trials of amifostine added to concurrent low-dose radiochemotherapy were identified in our literature search. While it is reasonable to extrapolate that the radioprotection of acute and chronic xerostomia with amifostine may extend to patients treated with low-dose concurrent chemoradiotherapy, there is the theoretical possibility that amifostine may compromise the anti-tumour effectiveness of low-dose daily cisplatin or carboplatin.

Second, the data on tumour control and survival outcomes support that amifostine does not confer tumour protection; however, long-term data beyond 24 months are not yet available.

Finally, the optimum dose and delivery of amifostine has yet to be determined. In the large trial reported by Brizel et al, a daily intravenous dose of 200 mg/m^2 15 to 30 minutes before radiotherapy was effective in reducing xerostomia; however, the smaller randomized trials support that different doses may confer a greater magnitude of benefit against both xerostomia and mucositis. The role of amifostine delivered subcutaneously warrants further investigation as it is a very attractive alternative but there is little evidence to advocate its use at this point. Timing and minimum dose of amifostine are also of interest. Of the two small trials that administered amifostine only on chemotherapy days, one trial detected a benefit of amifostine for patients in both xerostomia and mucositis, while the other did not.

In the context of current practice in Ontario, the efficacy of amifostine in cisplatin-based concomitant radiochemotherapy has yet to be fully established, and the practical logistics of delivering amifostine, cisplatin, and radiotherapy within a short time period in the cancer centres are substantial. Conversely, the demonstrated benefit of amifostine with the reduction in radiation-induced acute and chronic xerostomia makes it a possible treatment option for suitable cancer patients in Ontario.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

The Head and Neck Cancer Disease Site Group (DSG) is not aware of any evidence based on Canadian data that indicates whether the economic cost of amifostine is outweighed by the economic cost of toxic side effects when amifostine is not delivered.

An economic analysis reported data from a randomized trial of 28 patients. The analyst reports that, including the cost of amifostine, the mean per patient supportive care costs (in German Deutsche Marks [DM]) are significantly lower in patients who receive amifostine than those who do not receive the drug (DM4,401 versus DM5,873, p=0.02).

There is some evidence from one small trial to suggest that amifostine may be more cost-effective than providing increased supportive care without amifostine, but more data based on patients within the Canadian health care system is needed.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Practitioner feedback was obtained through a mailed survey of 52 practitioners in Ontario (12 medical oncologists, 24 radiation oncologists, and 16 surgeons). The survey consisted of 21 items evaluating the methods, results, and interpretive summary used to inform the draft recommendations outlined and whether the draft recommendations should be approved as a practice guideline. Written comments were invited. Follow-up reminders were sent at two weeks (post card) and four weeks (complete package mailed again). The results of the survey have been reviewed by the Head and Neck Disease Site Group (DSG).

The practice guideline report was circulated to 16 members of the Practice Guidelines Coordinating Committee (PGCC) for review and approval. Twelve of the 16 members convened to review and discuss the practice guideline. All 12 Practice Guidelines Coordinating Committee members approved the practice guideline report as written, with only minor modifications required.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

- On the basis of the available data, amifostine is recommended as an effective treatment option for the reduction of acute and chronic xerostomia associated with radical conventionally fractionated radiotherapy, given to patients in the head and neck region encompassing at least 75% of the parotid glands, with or without standard dose carboplatin.

- The recommended dose and administration of amifostine is an intravenous infusion 15 to 30 minutes prior to radiation, with standard doses of 500 mg or doses ranging from 200 mg/m^2 to 300 mg/m^2. The Head and Neck Cancer Disease Site Group would be supportive of randomized trials designed to compare amifostine delivered subcutaneously versus intravenously.
- Data on the protective effect of amifostine from mucositis are inconclusive at this time.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The recommendations are supported by randomized controlled trials and meta-analysis.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Original Guideline: May 2003

- The only large randomized trial detected a significant reduction in the severity of acute and chronic xerostomia but not mucositis, with amifostine added to radiotherapy for head and neck cancer.
- From the available data, pooled results across trials indicate that patients had significantly less acute and late xerostomia with amifostine added to radiotherapy or radiochemotherapy with standard dose carboplatin for head and neck cancer. There were no statistically significant differences in mucositis. Data from one randomized trial have yet to be presented.
- Results indicate that amifostine does not affect the anti-tumour effectiveness of radiotherapy with or without concurrent chemotherapy with carboplatin.

Update

- One small randomized trial comparing amifostine to control and one randomized trial comparing subcutaneous with intravenous amifostine administration were identified and included in the systematic review of the evidence.
- The first bullet has been revised through the editorial process to provide greater clarity and should now read:
    - Of the seven randomized trials comparing amifostine to control or placebo, only one trial randomized more than 100 patients per treatment arm. That trial detected a significant reduction in the severity of acute and chronic xerostomia but not mucositis, with amifostine added to radiotherapy for head and neck cancer.

- The last sentence of the second bullet has been revised through the editorial process to provide greater clarity and should now read:
    - Data from one randomized trial published as an abstract have yet to be presented.

POTENTIAL HARMS

Nausea, vomiting, hypotension, and allergic reactions were the most commonly reported side effects of amifostine, but they were rarely severe (≥grade 3).

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- For suitable patients with stage III/IV squamous cell carcinoma, a common practice in Ontario is a conventionally fractionated course of radiotherapy delivered concurrently with low-dose cisplatin or carboplatin. No trials of amifostine added to concurrent low-dose radiochemotherapy were identified in our literature search. While it is reasonable to extrapolate that the radioprotection of acute and chronic xerostomia with amifostine may extend to patients treated with low-dose concurrent chemoradiotherapy, there is the theoretical possibility that amifostine may compromise the anti-tumour effectiveness of low-dose daily cisplatin or carboplatin.
- The data on tumour control and survival outcomes support the conclusion that amifostine does not confer tumour protection; however, long-term data beyond 24 months are not yet available for this population of patients.
- Nausea, vomiting, hypotension, and allergic reactions were reported as the most common side effects of amifostine, but they were rarely severe (≥grade 3).
- Care has been taken in the preparation of the information contained in this document. Nonetheless, any person seeking to apply or consult these guidelines is expected to use independent medical judgment in the context of individual clinical circumstances or seek out the supervision of a qualified clinician. Cancer Care Ontario makes no representation or warranties of any kind whatsoever regarding their content or use or application and disclaims any responsibility for their application or use in any way.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Head and Neck Cancer Disease Site Group. Hodson DI, Browman GP, Thephamongkhol K, Oliver T, Zuraw L. The role of amifostine as a radioprotectant in the management of patients with squamous cell head and neck cancer [full report]. Toronto (ON): Cancer Care Ontario (CCO); 2004 Mar [online update]. 22 p. (Practice guideline report; no. 5-8). [26 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2003 Apr 9 (revised online 2004 Mar)

GUIDELINE DEVELOPER(S)

Practice Guidelines Initiative - State/Local Government Agency [Non-U.S.]

GUIDELINE DEVELOPER COMMENT

The Practice Guidelines Initiative (PGI) is the main project of the Program in Evidence-based Care (PEBC), a Province of Ontario initiative sponsored by Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

SOURCE(S) OF FUNDING

Cancer Care Ontario
Ontario Ministry of Health and Long-Term Care

GUIDELINE COMMITTEE

Provincial Head and Neck Cancer Disease Site Group

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

For a current list of past and present members, please see the Cancer Care Ontario Web site.

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Members of the Head and Neck Cancer Disease Site Group disclosed potential conflict of interest information.

GUIDELINE STATUS

This is the current release of the guideline.

The FULL REPORT, initially the full original Guideline or Evidence Summary, over time will expand to contain new information emerging from their reviewing and updating activities.

Please visit the Cancer Care Ontario Web site for details on any new evidence that has emerged and implications to the guidelines.

GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the Cancer Care Ontario Web site.

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- The role of amifostine as a radioprotectant in the management of patients with squamous cell head and neck cancer. Summary. Toronto (ON): Cancer Care Ontario. Electronic copies: Available in Portable Document Format (PDF) from the Cancer Care Ontario Web site.
- Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. J Clin Oncol 1995;13(2):502-12.

PATIENT RESOURCES

None available

NGC STATUS

This summary was completed by ECRI on January 23, 2004. The information was verified by the guideline developer as of February 25, 2004. This summary was updated by ECRI on May 21, 2004. The updated information was verified by the guideline developer on June 2, 2004.

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